

Residential Proximity to Agricultural Pesticide Use and Incidence of Breast Cancer in California, 1988–1997

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California is the largest agricultural state in the United States and home to some of the world's highest breast cancer rates. The objective of our study was to evaluate whether California breast cancer rates were elevated in areas with recent high agricultural pesticide use. We identified population-based invasive breast cancer cases from the California Cancer Registry for 1988–1997. We used California's pesticide use reporting data to select pesticides for analysis based on use volume, carcinogenic potential, and exposure potential. Using 1990 and 2000 U.S. Census data, we derived age- and race-specific population counts for the time period of interest. We used a geographic information system to aggregate cases, population counts, and pesticide use data for all block groups in the state. To evaluate whether breast cancer rates were related to recent agricultural pesticide use, we computed rate ratios and 95% confidence intervals using Poisson regression models, adjusting for age, race/ethnicity, and neighborhood socioeconomic status and urbanization. This ecologic (aggregative) analysis included 176,302 invasive breast cancer cases and 70,968,598 person-years of observation. The rate ratios did not significantly differ from 1 for any of the selected pesticide categories or individual agents. The results from this study provide no evidence that California women living in areas of recent, high agricultural pesticide use experience higher rates of breast cancer. *Key words:* breast neoplasms, geographic information system, incidence, pesticides. *Environ Health Perspect* 113:993–1000 (2005). doi:10.1289/ehp.7765 available via <http://dx.doi.org/> [Online 15 April 2005]

Breast cancer is the most common cancer among women in the United States (Parkin 2001) and the leading cause of cancer death among women 35–54 years of age (National Cancer Institute 2004). Fueled by concern over the concurrent increase in breast cancer incidence with the widespread emergence of large-scale agricultural pesticide use [U.S. Environmental Protection Agency (EPA) 2004], considerable research has been conducted on the relationship between pesticide exposures and breast cancer. Substantial evidence from laboratory and animal studies indicates that many pesticides are carcinogenic (Brody and Loriaux 2003; Crisp et al. 1997; Dich et al. 1997; Sherman 1994; U.S. EPA 2002) and/or xenoestrogens (Illinois EPA 1997; National Toxicology Program 2001; EXTOWNET 1998). The risks posed to human populations from low-level environmental contamination, however, are largely unknown. California, which boasts a \$25 billion agricultural industry, is the largest agricultural state in the United States [United States Department of Agriculture (USDA) 2003]; it is also home to some of the world's highest breast cancer rates (Parkin et al. 1997).

This study was initiated in response to growing concern about potential exposures to current pesticide applications among agricultural community residents (Solomon and Mott 1998). Using 10 years of statewide cancer registry data, linked to California's mandatory pesticide use reporting data, we evaluated whether breast cancer rates are higher among women living in areas with recent intense

agricultural pesticide use. With more than 176,000 breast cancer cases and nearly 71 million person-years of observation among an ethnically diverse population in a large agricultural state, this study offers sufficient detail and power to provide a broad initial overview of breast cancer incidence patterns and potential environmental exposures to agricultural pesticide use.

Materials and Methods

Cancer Incidence Data

We identified all invasive breast cancer cases diagnosed in women ≥ 20 years of age from the California Cancer Registry (CCR), for 1988 through 1997 ($n = 181,080$) (CCR 2005). Modeled after the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program, the CCR maintains the highest standards for data quality and completeness; their data are estimated to be 99% complete and include case sharing from neighboring states (Kwong et al. 2001). Case characteristics, including race, age, sex, and residence at time of diagnosis, are collected by the CCR from patients' medical records. Use of human subjects' data in this study was reviewed and approved by the California Health and Human Services Agency, Committee for the Protection of Human Subjects.

Geocoding

We assigned census block group designations to cases based on the geocoded location of residence at the time of diagnosis. We completed

this task using a geographic information system (GIS) to automatically match addresses with a road network and determine the corresponding census block group. When possible, we manually located all addresses that could not be automatically matched using the GIS. Because most addresses not automatically geocoded were post office boxes, we augmented our manual review with a mailed survey to U.S. postmasters, requesting street addresses for CCR records that contained only a post office box address (Hurley et al. 2003). Overall, we successfully geocoded 97.4% of cases (176,302 of 181,080) to a 1990 census block group [Geographic Data Technology (GDT) 2000; U.S. Census Bureau 1995].

Pesticide Data

California's Department of Pesticide Regulation maintains a pesticide use reporting (PUR) database that includes detailed information on all agricultural pesticide applications in the state, including the active ingredient, application method, quantity applied, acres treated, crop treated, and location (in square mile sections). Pesticides included in the PUR database include all insecticides, herbicides, fungicides, and fumigants applied for agricultural purposes. Full use reporting began in 1990; therefore, we used PUR data reported from 1990 through 1997 to calculate the annual average pesticide use in each square mile section of California (California Department of Pesticide Regulation 1998). For our analysis, we combined pesticides into six toxicologic groups and also selected five individual pesticides for examination based on their carcinogenic and exposure potential.

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Toxicologic groups of pesticides. More than 850 different pesticides were reported to the PUR system during our study period, making analysis of each individual pesticide impractical. Therefore, we combined pesticides into six toxicologic groups for our analysis: probable or likely carcinogens, possible or suggestive carcinogens, mammary carcinogens, xenoestrogens, cholinesterase inhibitors, and organochlorines. Some pesticides belong to more than one group. Table 1 lists the individual pesticides that comprise each of these groups. Our purpose for categorizing the pesticides was to study exposures to chemicals with similar toxicity end points relevant to breast cancer because, in reality, exposures occur to mixtures of chemicals and total risk may be underestimated by studying individual exposures.

California banned or severely restricted all pesticides classified as known human carcinogens before the time of this study. The carcinogenic evidence for the pesticides we assessed is based almost exclusively on laboratory animal studies (Crisp et al. 1997). Given these data, we combined 16 pesticides classified as probable or likely human carcinogens (U.S. EPA 2002). Similarly, we combined 35 pesticides classified as possible or suggestive human carcinogens (U.S. EPA 2002). We identified four pesticides as potential human mammary carcinogens, based on excess mammary tumors in laboratory animal studies (EXTOXNET 1998; U.S. EPA 2002). For the purpose of this study,

we defined xenoestrogens as any pesticides that directly or indirectly increase estrogenic effects and may ultimately lead to mammary cell proliferation. We identified 34 pesticides used in California as potential xenoestrogens (Crisp et al. 1997; EXTOXNET 1998; Illinois EPA 1997). We chose cholinesterase inhibitors as a category because they represent two specific pesticide groups—organophosphates and carbamates—both of which have the potential to increase estrogenic activity by acting on the hypothalamic-pituitary axis (Cabello et al. 2001; EXTOXNET 1998). We chose organochlorines as a category because of their persistence in the body and the environment and because of extensive evidence for estrogenicity (Snedeker 2001). We identified only three organochlorine pesticides as being used in California between 1990 and 1997. These pesticide groupings are the same as those used in an earlier study of breast cancer incidence in a large statewide cohort study (Reynolds et al. 2004b).

Selection of individual pesticides. We selected five pesticides for individual analysis: simazine, diuron, oryzalin, propargite, and methyl bromide. The first three have established toxicologic data from laboratory animal studies implicating their role in mammary tumorigenesis and are also considered xenoestrogens (Crisp et al. 1997; EXTOXNET 1998; Illinois EPA 1997; National Toxicology Program 2001; U.S. EPA 2002). We selected

the final two pesticides, propargite and methyl bromide, because they were the two top-ranking chemicals identified by our cancer hazard ranking system for pesticides, indicating they were the most widely used with the greatest exposure potential and likelihood of being carcinogenic in California during our study period.

Detailed methods for our cancer hazard ranking system for pesticides are presented elsewhere (Gunier et al. 2001). Briefly, we assigned each pesticide a hazard score based on two carcinogenicity measures (cancer class and potency) and two exposure potential measures (field volatilization flux and half-life). We then multiplied each pesticide's hazard score with the average annual pounds of that pesticide applied statewide from 1990 through 1997 to derive the cancer hazard-adjusted use. We identified 59 pesticides with $\geq 100,000$ lb/year used in California, for which all the necessary toxicity and environmental data were available. Methyl bromide and propargite ranked highest among these 59 pesticides for hazard-adjusted use during the time period of interest (1990–1997).

Pesticide exposure assessment. We used PUR data reported from 1990 through 1997 to calculate the annual average pesticide use in each square mile section of California (California Department of Pesticide Regulation 1998). Using a GIS (ArcView, version 3.0; Environmental Systems Research Institute Inc., Redlands, CA), we identified all square-mile sections located within each census block group. If a section fell into more than one block group, we allocated the pesticide use based on the percent area of the section in each block group. In 1990, California block groups had a median land area of 0.2 mi², with a range between 0.0001 and 3,610 mi² (U.S. Census Bureau 1995). We estimated the average annual agricultural pesticide use during the study period, for each block group, by summing the average pounds applied in all relevant sections and then dividing by the block group area to obtain pesticide use density in pounds per square mile.

Population data. We based our rate calculations on population estimates derived from census data compiled at the U.S. Census block group level. Inconsistencies in data collection between the 1990 and 2000 censuses required specialized development of denominator estimates. For this purpose, we obtained two customized data sets through special permission from the Census Activities and Tabulation Staff, Population Division, of the U.S. Census Bureau (U.S. Census Bureau, unpublished data). The two data sets, which contained mutually exclusive categories for race and Hispanic origin, consisted of block group counts of all women in California, ≥ 20 years of age, by race and Hispanic origin at 5-year

Table 1. Toxicologic categorization^a of agricultural pesticides used in California and reported to the PUR system, 1990–1997.

Toxicologic group	Individual pesticides				
Probable or likely human carcinogens	Cacodylic acid	Diclofop-methyl	Mancozeb	Propargite ^b	
	Captan	Diuron ^b	Maneb	Propyzamide	
	Chlorothalonil	Ethoprop	Metam sodium	Thiophanate-methyl	
	1,3-Dichloropropene	Iprodione	Orthophenylphenol	Ziram	
Possible or suggestive human carcinogens	Acephate	Chlorthal-dimethyl	Malathion	Permethrin	
	Acrolein	Cyanazine	Methidathion	Phosmet	
	Alachlor	Cypermethrin	Metolachlor	Piperonyl butoxide	
	Amitraz	Dicofol	Molinate	Propanil	
	Benomyl	Dimethoate	Norflurazon	Simazine ^b	
	Bifenthrin	Ethalfuralin	Oryzalin ^b	Triadimefon	
	Bromacil	Hydrogen cyanamide	Oxyfluorfen	Trifluralin	
	Bromoxynil octanoate	Lindane	Parathion	Vinclozolin	
	Carbaryl	Linuron	Pendimethalin		
	Mammary carcinogens	Atrazine	Diuron ^b	Oryzalin ^b	Simazine ^b
Xenoestrogens	Acrolein	2,4-D	Methidathion	Pendimethalin	
	Alachlor	Diuron ^b	Methomyl	Permethrin	
	Aldicarb	Endosulfan	Methyl bromide ^b	Simazine ^b	
	Atrazine	Hydrogen cyanamide	Metribuzin	Thiophanate-methyl	
	Benomyl	Iprodione	Mevinphos	Trifluralin	
	Bromacil	Lindane	Molinate	Vinclozolin	
	Cacodylic acid	Malathion	Oryzalin ^b	Ziram	
	Captan	Mancozeb	Paraquat dichloride		
	Dicofol	Maneb	Parathion		
	Cholinesterase inhibitors	Acephate	Diazinon	Malathion	Mevinphos
		Aldicarb	Dimethoate	Methamidophos	Naled
		Azinophos methyl	Disulfoton	Methidathion	Parathion
Carbaryl		Ethephon	Methomyl	Phorate	
Chlorpyrifos		Fenamiphos	Methyl parathion	Phosmet	
Organochlorines	Dicofol	Endrin	Lindane		

2,4-D, 2,4-dichlorophenoxyacetic acid.

^aSome pesticides fall into more than one group. ^bPesticide also chosen for individual analysis.

age increments, one from the 1990 Census and the other from the 2000 Census. After adjusting for differences in geographic boundaries and race designations between the two censuses, we used linear interpolation to estimate annual age- and race-specific population counts for all block groups in the state. The denominator used in the analysis is the summed annual age- and race-specific block group population counts for 1988 through 1997. A description of this process is presented in more detail elsewhere (Reynolds et al. 2005).

Covariate information. Race/ethnicity. We derived race/ethnicity information for the California population from the 1990 and 2000 Census data as described above. We obtained the race/ethnicity of cases from the CCR data. The categories used for analysis were non-Hispanic white, black, Hispanic, Asian/Pacific Islander, and other. The “other” category included American Indian, other, and non-specified groups.

Socioeconomic status and urbanization. We characterized the socioeconomic status (SES) and degree of urbanization of every census block group in California using additional 1990 census data (U.S. Census Bureau 1992). We created a summary SES metric incorporating occupation, education, and income. To do this, we first ranked all California block groups separately by education level (percentage of adults ≥ 25 years of age completing a college degree or higher), income (median family income), and occupation (percentage of adults employed in managerial/professional occupations) according to quartiles, based on the statewide adult population. This resulted in a score of 1–4 for each of these SES attributes. We then created a summary SES metric by summing the scores across each of the four SES attributes and categorizing them into four groups (high to low), based on the quartiles of this score. Because this SES metric was based on all adults (not just women) and because of differential population growth across California block groups since 1990, the person-years in our study do not distribute evenly across SES quartiles.

To define the degree of urbanization, we used a combination of census-based information. The U.S. Census Bureau defines an urbanized area as a centralized area, with a population of $\geq 50,000$ people and a population density of at least 1,000 people per square mile (U.S. Census Bureau 2002a). Because, by this definition, 85% of California residents live in an urban area, we used additional information to refine the urbanization measure. Our categorization, which we based primarily on population and ultimately refined with population density, included four values: “metropolitan urban” represented block groups with the highest quartile of population

density within U.S. Census–defined urbanized areas (i.e., population $> 1,000,000$); “metropolitan suburban” included the rest of the population within census-defined urbanized areas; “city” included census-defined places with $> 50,000$ people, outside of an urbanized area; and “small town/rural” included census-defined places with $< 50,000$ people outside of an urbanized area.

Age group. We obtained age at diagnosis from the CCR and categorized women into 5-year age groups for covariate adjustment in regression models. There is substantial evidence that risk factors for breast cancer are somewhat different for pre- versus postmenopausal diagnoses (de Waard 1998). Unfortunately, information on menopausal status was not available for either the cases or the statewide population. To evaluate whether risks associated with pesticide use density differed for pre- and postmenopausal breast cancer incidence, we used age at diagnosis as a proxy for menopausal status and created three groups: 20–44 years of age to approximate a premenopausal group, 45–54 years of age to represent an approximate perimenopausal group, and ≥ 55 years of age as a proxy for postmenopausal women (National Cancer Institute 2003). We did not include these broad age categories in the regression models as covariates but rather used them only to stratify the data.

Analysis

Because our toxicologic groupings and individual pesticides were highly correlated, and not necessarily mutually exclusive, we looked at the six pesticide groupings and five individual pesticides in separate statistical models. For each group or individual pesticide, we considered block groups with pesticide use density of $< 1 \text{ lb/mi}^2$ to have negligible exposure potential; these served as our reference category or “unexposed” group. We based our other three pesticide use categories on the distributions of pesticide use densities among subjects with $\geq 1 \text{ lb/mi}^2$ of use density: 1st–49th percentiles, 50th–74th percentiles, and ≥ 75 th percentile.

We computed rate ratios and 95% confidence intervals (CIs) using Poisson regression models run with the GENMOD procedure in SAS (version 8.0e; SAS Institute Inc., Cary, NC). We calculated rate ratios for each level of pesticide use density for the six pesticide groupings and five individual pesticides, initially adjusting for age and race. Subsequent models also adjusted for neighborhood SES and urbanization. Our previous work with these data, and that of others, indicated that the breast cancer risk associated with SES varies by race/ethnicity (Reynolds et al. 2005; Yost et al. 2001). Therefore, our final regression models also contained a multiplicative interaction term for race/ethnicity and SES. We then repeated these analyses, stratifying by age

group and degree of urbanization (urban, suburban, city, small town/rural) to evaluate potentially different risk relationships among these subgroups. We performed all analyses with SAS.

Initial evaluations of the deviance and Pearson chi-square generalized statistics from our Poisson models suggested overdispersion in our data (SAS Institute Inc. 1999). Such overdispersion can result from sparse data, variations in an assumed constant rate of event occurrence, and/or unexplained heterogeneity and can lead to biased estimates of the standard errors in Poisson regression (Barron 1992). Employing a rescaling approach to address issues of overdispersion in our data, we multiplied the covariance matrix by a dispersion parameter, which was estimated based on the Pearson chi-square statistic (McCullagh and Nelder 1989; SAS Institute Inc. 1999). This adjustment does not change the risk estimates, but inflates the standard errors to adjust for overdispersion. We also evaluated an alternative approach for modeling the data using negative binomial regression, a generalization of the Poisson model that incorporates heterogeneity (Barron 1992). Because the results from the two methods were essentially the same, we have reported the results from the Poisson models run with the rescaled standard errors. This seems to be the more familiar statistical approach and is the one recently employed in a Marin, California, breast cancer study (Benz et al. 2003).

Results

This analysis included 176,302 invasive breast cancer cases among the California adult female population, with 70,968,598 person-years of observation. Table 2 shows the distribution of selected characteristics for the breast cancer cases and the California adult female population for the study period (1988–1997). As expected, cases were more likely than the adult female statewide population to be older and non-Hispanic white. Cases were also slightly more likely than the general population to live in suburban and higher SES neighborhoods. Previously published age-adjusted rate ratios for these demographic factors among this study population were consistent with other published data on these factors (Reynolds et al. 2005).

Table 3 shows the distribution of annual agricultural pesticide use density among the California census block groups included in these analyses. The number of block groups in the study with annual pesticide use density of $\geq 1 \text{ lb/mi}^2$ for a given pesticide group ranged from 1,633 (8% of block groups) for organochlorines to 7,871 (37% of block groups) for xenoestrogens. The highest use density was for xenoestrogens, with a median application rate of 42 lb/mi^2 . For individual

pesticides, the number of block groups in the study with annual pesticide use density ≥ 1 lb/mi² for a given pesticide ranged from 1,823 (9% of block groups) for diuron to 4,100 (19% of block groups) for methyl bromide. The highest use density was for methyl bromide, with a median annual application rate of 125 lb/mi².

Table 4 presents the rate ratios obtained from the Poisson regression models predicting breast cancer risk associated with residential proximity to agricultural pesticide use. In the models adjusting for only age and race, point estimates for all use densities above the referent (< 1 lb/mi²) were < 1 for all groupings and individual pesticides considered, and in many cases, the 95% CIs included 1. Although the

age- and race-adjusted rate ratios for simazine, oryzalin, propargite, and methyl bromide were all significantly < 1 , additional adjustment for neighborhood SES and urbanization resulted in point estimates that did not significantly differ from 1. Likewise, in the fully adjusted models none of the rate ratios significantly differed from unity for any of the groupings or individual pesticides considered at any exposure level.

We repeated the Poisson regression analyses, stratifying separately by age group and neighborhood urbanization. We observed no substantial differences in risk estimates among the different age groups (data not shown) or by degree of neighborhood urbanization (data not shown).

Table 2. Distribution of selected characteristics for invasive breast cancer cases ($n = 176,302$) and the California adult female population, 1988–1997 (person-years, $n = 70,968,598$).

Characteristic	Cases (%)	Person-years (%)
Age (years)		
20–39	6.5	16.4
40–44	7.2	16.1
45–49	9.7	12.9
50–54	9.5	10.6
55–59	9.5	8.9
60–64	10.8	8.3
65–69	12.7	8.0
70–74	12.3	6.6
75–79	10.0	5.4
80–84	6.7	3.6
≥ 85	5.1	3.3
Race/ethnicity		
Non-Hispanic white	77.6	63.6
African American	5.7	6.3
Hispanic	10.2	19.6
Asian, Pacific Islander	5.7	9.7
Native American/other	0.8	0.8
Neighborhood SES ^a		
Low	13.4	18.4
Medium-low	25.5	27.4
Medium-high	29.7	28.5
High	31.3	25.7
Neighborhood urbanization ^b		
Metropolitan urban (most dense)	20.8	24.7
Metropolitan suburb	50.3	45.8
City	15.1	14.9
Small town/rural	13.8	14.6

^aBased on the distribution of the California census block–group levels of a census-based socioeconomic summary metric incorporating education, income, and occupation (see “Covariate information” for further explanation), and excludes a small number of cases without SES attribute data ($n = 49$). ^bUrbanization based on census block–group characteristics (see “Covariate information” for further description).

Table 3. Distribution of annual average agricultural pesticide use density (lb/mi²) in California census block groups with application ≥ 1 lb/mi² between 1990 and 1997.

Pesticides/pesticide groups	Block groups ^a [n (%)]	Median	75th percentile	Maximum
Probable or likely human carcinogens	5,626 (26)	30	221	25,383
Possible or suggestive human carcinogens	7,004 (33)	19	110	3,628
Mammary carcinogens	3,600 (17)	15	52	1,917
Xenestrogens	7,871 (37)	42	354	96,227
Cholinesterase inhibitors	6,752 (31)	19	114	6,454
Organochlorines	1,633 (8)	6	20	317
Simazine	2,252 (10)	12	39	1,856
Diuron	1,823 (9)	11	28	492
Oryzalin	2,209 (10)	9	25	473
Propargite	2,270 (11)	18	64	1,151
Methyl bromide	4,100 (19)	125	669	84,464

^aTotal number of census block groups included in the analysis was 21,515.

Discussion

This study represents a broad assessment of the relationship between agricultural pesticide use patterns and breast cancer incidence in women in a large and diverse agricultural state. The results provide no evidence that women living in areas of recent, high agricultural pesticide use experience higher breast cancer incidence rates. This lack of association was evident for all three age groups examined and did not differ between women living in urban and rural areas.

Much of the epidemiologic research on this topic has focused on examining the relationship between breast cancer and body burden levels of organochlorine pesticides (as measured in serum or adipose). Generally, results from these types of studies have been null (Adami et al. 1995; Calle et al. 2002; Laden et al. 2001; Safe 1997; Snedeker 2001; Wolff and Weston 1997), although a few well-designed studies have reported positive associations (Aronson et al. 2000; Hoyer et al. 1998, 2000; Romieu et al. 2000). One of the notable limitations of these studies, however, has been that they were able to evaluate only the relatively small number of compounds that are persistent and detectable by current analytic methods, with most focused on dichlorodiphenyltrichlorethane (DDT) or its metabolite dichlorodiphenyldichloroethylene (DDE) (Bagga et al. 2000; Charlier et al. 2003; Cocco et al. 2000; Dewailly et al. 1994; Falck et al. 1992; Hunter et al. 1997; Krieger et al. 1994; Laden et al. 2001; Lopez-Carrillo et al. 1997; Mendonca et al. 1999; Millikan et al. 2000; Olaya-Contreras et al. 1998; Romieu et al. 2000; Schecter et al. 1997; Unger et al. 1984; van't Veer et al. 1997; Wassermann et al. 1976; Wolff et al. 1993, 2000; Zheng et al. 1999). Furthermore, many of these studies have measured these compounds in blood or adipose collected at the time of diagnosis, which may not reflect exposures occurring during more etiologically relevant time periods, such as prenatal or adolescent growth (Potischman and Troisi 1999). Although the exposure estimates used in our analysis can account for a broader spectrum of potentially suspect agents, our lack of residential history information poses the same temporal limitation.

Occupational studies on this issue are quite mixed, with some suggesting a positive association between breast cancer and work-related pesticide exposures (Band et al. 2000; Duell et al. 2000; Gardner et al. 2002; Kogevinas et al. 1997) and others reporting no association (Dolapsakis et al. 2001; Fleming et al. 1999, 2003; MacLennan et al. 2003; Sperati et al. 1999; Wang et al. 2002; Weiderpass et al. 1999; Zhong and Rafnsson 1996) or even a protective effect (Kristensen et al. 1996; Settimi et al. 1999). These studies, however, have been limited by small numbers of women,

an inability to control for other breast cancer risk factors, reliance on sometimes crude proxy measures of exposure and potential “healthy worker” biases in cohort studies using external population comparisons.

Similar to our study, a number of ecologic (aggregative) analyses have been conducted to examine the potential relationship between environmental exposures to agricultural pesticide use and breast cancer (Abdalla et al. 2003; Brody et al. 2004; Hopenhayn-Rich et al. 2002;

Janssens et al. 2001; Kettles et al. 1997; O’Leary et al. 2004; Reynolds et al. 2004b; Safi 2002; Schreinemachers 2000; Schreinemachers et al. 1999; Wesseling et al. 1999). Again, the results from these studies are mixed, with some suggesting a positive association (Brody et al. 2004; Janssens et al. 2001; Kettles et al. 1997; O’Leary et al. 2004; Wesseling et al. 1999) and others not (Abdalla et al. 2003; Hopenhayn-Rich et al. 2002; Reynolds et al. 2004b; Schreinemachers 2000; Schreinemachers et al. 1999).

A number of limitations common to ecologic (aggregative) studies are worth noting. Because data are summarized for groups of individuals, inferences can be made only about populations rather than individuals (Greenland and Morgenstern 1989; Morgenstern 1995, 1998). The primary limitation of such study designs is that the heterogeneity of exposure and covariate levels within groups is not fully captured with ecologic data. This can lead to ecologic effect estimates that do not reflect the

Table 4. Rate ratios (RR) of invasive breast cancer incidence associated with agricultural pesticide use density in California census block groups.

Pesticide use level	Cases (n)	Person-years (n)	Adjustment for age, race		Adjustment for age, race, urban, SES, race × SES	
			RR	(95% CI)	RR	(95% CI)
Probable or likely human carcinogens						
< 1 lb/mi ² (low)	128,931	51,336,520	1.00		1.00	
1st–49th percentile	26,153	10,484,707	0.98	(0.96–1.00)	1.00	(0.98–1.02)
50th–74th percentile	11,718	4,878,498	0.93	(0.90–0.96)	0.98	(0.95–1.01)
≥ 75th percentile (high)	9,500	4,268,872	0.89	(0.86–0.93)	1.00	(0.96–1.04)
Possible or suggestive human carcinogens						
< 1 lb/mi ² (low)	117,492	46,546,867	1.00		1.00	
1st–49th percentile	31,964	13,065,368	0.96	(0.90–1.04)	0.98	(0.91–1.06)
50th–74th percentile	15,124	6,153,979	0.96	(0.87–1.06)	1.00	(0.90–1.12)
≥ 75th percentile (high)	11,722	5,202,383	0.89	(0.80–1.00)	1.00	(0.87–1.13)
Mammary carcinogens						
< 1 lb/mi ² (low)	147,214	58,855,965	1.00		1.00	
1st–49th percentile	15,912	6,530,669	0.96	(0.94–0.98)	1.00	(0.98–1.02)
50th–74th percentile	6,951	2,904,907	0.92	(0.89–0.95)	0.99	(0.96–1.03)
≥ 75th percentile (high)	6,225	2,677,057	0.90	(0.87–0.94)	1.01	(0.97–1.04)
Xenoestrogens						
< 1 lb/mi ² (low)	109,452	43,326,975	1.00		1.00	
1st–49th percentile	35,670	14,494,059	0.96	(0.85–1.09)	0.99	(0.87–1.12)
50th–74th percentile	16,568	6,814,729	0.95	(0.80–1.12)	0.99	(0.83–1.18)
≥ 75th percentile (high)	14,612	6,332,834	0.92	(0.77–1.10)	0.99	(0.82–1.20)
Anticholinesterase						
< 1 lb/mi ² (low)	119,297	47,384,054	1.00		1.00	
1st–49th percentile	31,250	12,682,529	0.98	(0.85–1.13)	0.99	(0.85–1.16)
50th–74th percentile	14,509	5,879,649	0.96	(0.78–1.18)	1.00	(0.81–1.24)
≥ 75th percentile (high)	11,246	5,022,366	0.89	(0.71–1.12)	0.99	(0.77–1.28)
Organochlorines						
< 1 lb/mi ² (low)	164,583	65,912,011	1.00		1.00	
1st–49th percentile	6,698	2,759,649	0.94	(0.91–0.98)	0.99	(0.96–1.03)
50th–74th percentile	2,739	1,183,156	0.91	(0.86–0.96)	0.99	(0.94–1.05)
≥ 75th percentile (high)	2,282	1,113,781	0.85	(0.79–0.90)	0.98	(0.92–1.04)
Simazine						
< 1 lb/mi ² (low)	158,302	63,559,811	1.00		1.00	
1st–49th percentile	9,452	3,845,789	0.95	(0.92–0.99)	1.00	(0.96–1.04)
50th–74th percentile	4,504	1,861,051	0.93	(0.88–0.98)	1.00	(0.95–1.06)
≥ 75th percentile (high)	4,044	1,701,947	0.92	(0.87–0.97)	1.01	(0.95–1.07)
Diuron						
< 1 lb/mi ² (low)	162,056	64,939,678	1.00		1.00	
1st–49th percentile	7,696	3,233,201	0.91	(0.53–1.58)	0.99	(0.55–1.78)
50th–74th percentile	3,440	1,461,717	0.91	(0.40–2.04)	1.00	(0.43–2.37)
≥ 75th percentile (high)	3,110	1,334,001	0.91	(0.39–2.12)	1.00	(0.40–2.45)
Oryzalin						
< 1 lb/mi ² (low)	159,984	64,007,899	1.00		1.00	
1st–49th percentile	8,948	3,676,123	0.96	(0.93–0.99)	1.00	(0.98–1.03)
50th–74th percentile	3,977	1,753,630	0.91	(0.87–0.95)	0.99	(0.95–1.04)
≥ 75th percentile (high)	3,393	1,530,947	0.88	(0.84–0.92)	0.99	(0.95–1.04)
Propargite						
< 1 lb/mi ² (low)	159,937	63,771,900	1.00		1.00	
1st–49th percentile	9,241	3,984,021	0.93	(0.90–0.96)	0.98	(0.95–1.01)
50th–74th percentile	4,080	1,797,236	0.90	(0.86–0.94)	0.99	(0.95–1.03)
≥ 75th percentile (high)	3,044	1,415,441	0.86	(0.82–0.91)	1.00	(0.95–1.06)
Methyl bromide						
< 1 lb/mi ² (low)	142,062	56,718,156	1.00		1.00	
1st–49th percentile	17,334	7,145,385	0.95	(0.93–0.97)	0.98	(0.95–1.00)
50th–74th percentile	8,535	3,621,535	0.95	(0.92–0.98)	0.99	(0.96–1.02)
≥ 75th percentile (high)	8,371	3,483,522	0.96	(0.93–0.99)	1.02	(0.99–1.05)

biologic effect at the individual level—commonly referred to as “ecologic bias” (Greenland and Morgenstern 1989; Morgenstern 1995, 1998). Although our study, by virtue of its design, cannot completely escape this limitation, the small unit of analysis used in our study helps reduce the within-group heterogeneity. Ecologic studies such as this one, however, have a number of advantages as well (Morgenstern 1995, 1998; Walter 1991). By using monitoring data, ecologic studies can estimate potential ambient exposures that do not lend themselves to subject recall. Furthermore, our study population was large and geographically dispersed. This provided variability in potential exposures not often available from other epidemiologic study designs. The variability in exposure and large sample size combine to offer statistical power sufficient to detect small risks that, if large numbers of people are exposed, may be very important from a public health standpoint. Thus, although our study certainly has some limitations, it also offers some advantages over other traditional epidemiologic study designs.

Our study has a number of advantages over many of the ecologic studies conducted to date. Because ours was a study of incidence rather than mortality, we could more directly evaluate potential risk relationships without potential confounding by factors related to prognosis. We were able to evaluate classes of chemicals and individual chemicals of interest specific to breast cancer, whereas many of the previous studies relied on measures that are more global (e.g., total pounds of all pesticides applied) or used acreage of specific crop types as proxy measures for classes of pesticide exposures. Additionally, we were able to evaluate pesticide applications on a small scale (census block group); most other ecologic studies have estimated exposures over larger areas, such as counties—a method that is likely to result in greater exposure misclassification (Rull and Ritz 2003).

The ability to control for area differences in SES and urbanization is especially important, given that regions of intense agricultural pesticide use are often rural and of low SES, whereas breast cancer rates tend to be higher in upper SES (Hall and Rockhill 2002; Heck and Pamuk 1997; Reynolds et al. 2005; Teppo 1984; Yost et al. 2001) and more urban areas (Doll 1991; Mahoney et al. 1990; Reynolds et al. 2005). Because lifestyle factors related to breast cancer risk, such as physical activity, smoking, alcohol consumption, and childbearing patterns, are likely to differ between rural and urban areas in a way that would favor lower breast cancer rates in rural areas, where pesticide use is typically high (Reynolds et al. 2004a), it is essential to account for urbanization in analyses of breast cancer and agricultural pesticide use. Because of our study’s large size, we were

able to evaluate pesticide use and breast cancer separately among rural and urban women.

The results from our study agree with an earlier analysis of agricultural pesticide use we performed among members of the California Teachers Study (CTS) cohort (Reynolds et al. 2004b). The CTS, a cohort of nearly 134,000 female California professional school employees geographically dispersed throughout the state, was specifically designed to study breast cancer (Bernstein et al. 2002). Thus, in the CTS analysis we were able to adjust for known breast cancer risk factors, something we were not able to do in this statewide study. Furthermore, in the CTS analysis, we estimated potential pesticide exposures at a very small scale (within a half-mile radius for each individual). Evaluating the same toxicologic categorizations and individual pesticides as in the statewide study, we saw no evidence of an association with recent pesticide use and breast cancer incidence within the CTS cohort (Reynolds et al. 2004b).

Both the statewide study presented here and our earlier analysis in the CTS cohort, are limited in that they are designed to determine whether breast cancer rates are higher in areas with recent high agricultural pesticide use. The results from both studies suggest not. The lack of an association in these studies, however, reflects only on reasonably concurrent exposure/outcome relationships and does not account for sources of broader exposures to pesticides or time windows of potential vulnerability. Furthermore, evaluating the long-term health effects of exposure to a single pesticide is difficult at the population level because of relatively low exposure levels, uncertainty regarding those exposure levels, and the use of many pesticides simultaneously in some census block groups.

Unfortunately, preexisting historical data on agricultural pesticide use, in conjunction with data on residential histories for those with or at risk of breast cancer, are neither readily available nor easy to collect. In California, agricultural pesticide use has been fairly consistent statewide, with basically the same counties, crops, and pesticides ranking highest in use year after year since full reporting was implemented in 1990 (Wilhoit et al. 1998). Reporting was not required for all agricultural pesticide use in the 1980s, but the restricted pesticide use reporting data indicate a similar consistency of rankings throughout the decade (California Department of Pesticide Regulation 2000). GIS mapping of pesticide use patterns in the 1980s compared with the 1990s, however, showed there has been some change at the neighborhood level because former cropland and surrounding buffers have been turned into residential areas.

Although the U.S. Census Bureau provides data on residential stability for households

but not for individuals, these data suggest a fairly mobile population in California. Census 2000 data indicate that only 31% of occupied California households in 2000 were occupied by the same householder for more than 10 years (U.S. Census Bureau 2002b). A previous analysis of participants in a breast cancer study among a cohort of California teachers, however, reported that residential stability may be greater among older women and women living in high SES neighborhoods (Hurley et al. 2005).

The inability to incorporate information on residential mobility and historical use patterns in this study introduces an important source of potential exposure misclassification. Although this limits our ability to evaluate etiologic relationships, our study was designed in response to public concern about exposures to current agricultural pesticide applications (Solomon and Mott 1998). Our results indicate that women living in areas of intense, recent agricultural pesticide use do not have higher breast cancer rates. Determining whether girls or young women living in these areas will be at greater risk of breast cancer in future years is a topic of continuing interest but beyond the scope of our study.

Recently, results were published from two case-control studies that tried to address the issue of historical agricultural pesticide exposures and breast cancer (Brody et al. 2004; O’Leary et al. 2004). A small case-control study ($n = 105$ cases) nested within a cohort of long-term residentially stable women living on Long Island, New York, used several different data sources to estimate historical exposures to agricultural pesticides (O’Leary et al. 2004). The authors reported an increased breast cancer risk associated with residence within a mile of a hazardous waste site containing pesticides [odds ratio (OR) = 2.9; 95% CI, 1.1–7.2] but no association with measures of residence on or near prior agricultural land (OR = 1.5; 95% CI, 0.8–2.9) or pesticides detected in drinking water (OR = 1.2; 95% CI, 0.6–2.1). These proxy exposure measures were not highly correlated, perhaps because they represent very different kinds of exposures and/or because of nonconcurrent time periods of measurement.

In a population-based case-control study of women living in Cape Cod, Massachusetts, exposure estimates were constructed dating back to 1948 from historical aerial photography and written pesticide spraying records (Brody et al. 2002, 2004). Although the authors reported no overall association between pesticide use and breast cancer, modest (although not statistically significant) associations were reported for aerial applications of persistent pesticides on cranberry bogs and less persistent pesticides applied for tree pests or agriculture (Brody et al. 2004). The Cape Cod study

probably represents the most comprehensive evaluation of historical agricultural pesticide applications and breast cancer risk conducted to date, and it illustrates the complexity of constructing these kinds of risk indicators. Through GIS, the Cape Cod study was able to estimate the relative intensity of pesticide exposures associated with residences over a ≥ 40 -year time span. Unlike our study, however, the Cape Cod study had limited variability in pesticide use and was not able to evaluate specific individual (or classes of) chemicals of interest.

The question of whether exposures to agricultural pesticide applications are a cause of breast cancer is obviously complex and likely to be answered only through a variety of complementary approaches. The recent advent of GIS-based technologies has enhanced our ability to characterize ambient exposures that are not easily reportable, or identifiable, on an individual basis. Studies that use GIS to integrate information across various domains, such as those being conducted on Long Island and Cape Cod, will be greatly improved by the availability of more comprehensive geographically referenced historical exposure data as they become available in the future.

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